The influence of formula Ma-Huang-Fu-Zi-Xi-Xin-Tang (Mao-bushi-saishin-to ;Mbst) on the results of urodynamic studies

Yoshizumi AOKI,[*a)] Kosuke UEDA,[b)] Kiichiro TSUTANI,[c)] and Kenjiro KOHRI[b)]

[a)]*Aoki Clinic, 1-11-4 2F-12, Umeda, Kita-ku, Osaka City, Osaka 530-0001, Japan.*
[b)]*Department of Urology, Nagoya City University Medical School, Kawasumi 1, Mizuho-ku, Nagoya City, Aichi 467-8601, Japan.*
[c)]*Department of Pharmacoeconomics, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.*

(Received April 11, 2001. Accepted October 5, 2001.)

Abstract

Objective: We showed that an ephedrine-containing Kampo medicine does not worsen urodynamic studies in younger and elderly persons, although ephedrine has sympathomimetic effects in pharmacology.

Method: A crossover trial on the effect of urodynamic study by *Ma-Huang-Fu-Zi-Xi-Xin-Tang* capsules (Mbst) and placebo (P) capsules based on the results of urodynamic studies was performed with 13 younger volunteers (38.0 ± 6.0, range 31-47). The mean prostate gland weight of the subjects was 15.6 ± 6.9g. Mbst was prepared as an example of an ephedrine containing drug. Uroflowgraphy was performed before Mbst or P administration and 3 hours after administration. The peak flow (Qmax), average flow (Qave), and voiding efficiency ε=Qave/Qmax. After we had checked the safety of performing this experiment with asymptomatic volunteers by performing the above experiments, we compared the urodynamic studies before and after administration of Mbst in elderly persons.

Results: The ε=Qave/Qmax after administration of Mbst or P was 0.66±0.08 or 0.65±0.09, respectively. Qmax and Qave showed no statistical differentiations respectively. Thus, no effect of the medicine was revealed for any end-points. The statistical power of ε=Qave/Qmax was 99%, compared to 45% for Qmax and 42% for Qave, which means that ε=Qave/Qmax appeared to be one of the strongest indicators for urinate disturbances.

Conclusion: Ephedrine containing Mbst was found to have little effect statistically on uroflowgraphy to have not only in younger subjects but also in elderly subjects. In addition, voiding efficiency ε=Qave/Qmax is a useful factor in the evaluation of urethral stenosis.

Key words ephedrine, cross-over test, ANOVA, urodynamic study, ε=Qave/Qmax.

Introduction

Purified ephedrine is used for bronchitis, asthma, hypotension, or the common cold for patients with benign prostate hyperplasia (BPH) ; it is difficult to anticipate the urinate disturbance and nocturia.[1)] It is well known that anti-cholinergic agents such as butylscopolamine may cause disturbance of normal bladder tonus.[2)] On the other hand, Diokno and Taub reported that sphincter disturbance can be improved by ephedrine.[3)]

Although ephedrine as an sympathomimetic agent and has no indication for patients with urinate disturbances, we have often seen the improvement of urinate failure in latent BPH patients after administration of some ephedrine-containing Chinese medicines.

In order to confirm the above observation, we first performed a double blind matched pair urodynamic study using a healthy volunteers study. Next, we performed further studies using elderly volunteers. We evaluated the influence of this ephedrine-containing Chinese traditional medicine on urination.

*To whom correspondence should be addressed. e-mail : aokidr@apricot.ocn.ne.jp

Subjects and Methods

Subjects for study

Preliminary urodynamic studies were performed using 13 male volunteers for determination of the minimum number of subjects necessary for the experiment. The median age of the subjects was 38.0 ± 6.0 years (mean±S.D., ranging from 31 to 47 years). The mean prostate gland weight was 15.6 ± 6.9 g, as calculated using ultrasonography. The ultrasonoscope (Aloca 640E. Aloca Co., Ltd. Osaka, Japan) was used in order to both measure the volumes of the prostate glands of the volunteers and to evaluate any organ disorders.

We could find no difference of reaction by Mbst between relatively infirm persons and relative healthy persons. And we could find no persons who complained of chills or cold feelings before and after this study.

A urodynamic study, ultrasonography, and blood examinations (GOT, GPT, γ-GTP, BUN, creatinin, serum electrolytes) were performed to choose healthy persons for this study. In particular, we made sure there was no residual urine volume or abnormal prostate morphology by performing ultrasonography. All volunteers gave written informed consent. We obtained voiding volumes (VV.) of 172.5±114.1 ml, voiding times (VT) of 16.95±6.85 sec, peak flows (Qmax) of 15.69±8.02 ml/sec, average flows (Qave) as 10.42±5.58 ml/sec, and voiding efficiencies (ε=Qave/Qmax)[4] as 0.665±0.05.

When the number of subjects was more than 5, we were able to maintain an accuracy of a=0.05, 1-b=0.8, Δ=0.2. However, we decided to use all 13 volunteers in order to widen the range of voiding efficiencies (ε=Qave/Qmax) by varying the influence of the individual effects of the medicine in this study.

In the second study, we compared the urodynamic factors before and after drug administrations in elderly volunteers. The 6 elderly persons used in this study were 65.4 ± 5.9 years old (mean±S.D., ranging from 50 to 63 years). The mean prostate gland weight was 21.9 ± 3.5 g, as calculated by ultrasonography.

We asked patients who had consulted Aoki Clinic or Nagoya City University for treatment of bronchitis and then had no urinary system side-effects by administration of Mbst, to take part in this study. We are grateful for their participation in this study.

Medicines

Ma-Huang-Fu-Zi-Xi-Xin-Tang capsules (Mbst : 麻黄附子細辛湯 capsule, produced by Kotaro-Pharmaceuticals Co., Ltd., Osaka, Japan) were prepared as an example of an ephedrine containing medicine, and placebo capsules (P) that were indistinguishable from the true medicine at a glance were also prepared. Two Mbst capsules, as a draft, contained 10.0 mg of ephedrine with pseudo-ephedrine as measured by HPLC. The total capsule net weight was 280 mg both for the medicine and the placebo. Two capsules of either medicine or placebo were administrated by mouth.

Protocol

We performed 2 studies with an interval of 4 weeks between administrations of the true medicine and placebo. Volunteers were randomly divided into 2 groups, and the cross over design was used, i.e., one group was administered the true medicine (Mbst) in the first study and the other in the second study as indicated in Figure 1.

We established washing out periods before both measurements, during which no medicine was administered for 7-days periods, and the volunteers were instructed to avoid tobacco and caffeine for 24 hours before each study. Water intake was not restricted for volunteers after the administration of medicine, and volunteers were instructed to drink non-caffeinated, non-alcoholic drinks, or water with their food. Uroflowgraphys were performed before medicine or placebo administration and 3 hours after administration.

In the study using elderly persons, the subjects were instructed to avoid tobacco and caffeine for 24 hours before the studies. Water intake was not restricted for volunteers after administration of medicine, and volunteers were permitted to drink non-caffeinated, non-alcoholic drinks, or water with their food. Then we

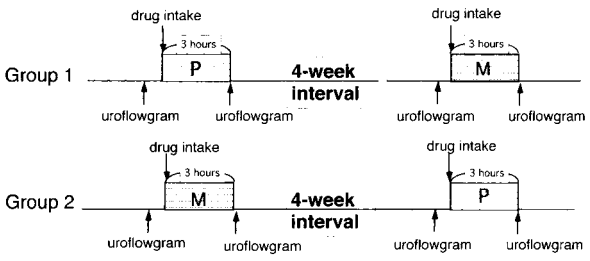

Figure 1. Protocol of this study shows when we obtained uroflowgrams before and after each administration. (M : *Ma-Huang-Fu-Zi-Xi-Xin-Tang* capsules. P:placebo) Group1 was administrated placebos 4 weeks after M, group 2 was administrated M after placebo.

obtained uroflowgraphys before and after administration once for each volunteer.

All studies were conducted between 1995 to 1997, so we thought no problem would occur with informed consent. We were delayed in publishing this study because our conception of the studies in order to prove of poor co-effects could hardly bring about the understanding.

Uroflowgraphy

Voiding volumes, peak flows, and average flows were determined using the uroflowmeter (UFS1005TP: Medical Measurement Systems Co., Ltd., Holland).

In the studies, we evaluated the peak flow (Qmax), average flow (Qave), and voiding volume (VV) and voiding time (VT) for each subject and evaluated voiding efficiency ε=Qave/Qmax both before and 3 hours after administration of 2 capsules. In addition, the total urine volume for 3 hours starting immediately after administration of medicine was determined, since the peak of blood concentration of ephedrine is reached 3 hours after administration of Mbst,[6] and the time of the second urodynamic measurement in all studies is 3 hours after administration.

Statistical analysis

We chose the peak flow (Qmax), average flow (Qave) and ε =Qave/Qmax as primary endpoints. Accordingly, we evaluated the total voiding volume (VV) 3 hours after capsule administration as secondary endpoints. Statistical analysis was performed by analysis of variance (ANOVA) to determine the contribution 2 factor of the medicine and the order of treatments.

In the study for elderly persons, we performed statistical analysis by matched pair t-tests on each endpoint between prior and following administration of Mbst.

Results

We analyzed the 3 factors Qmax, Qave, and ε=Qave/Qmax from the urodynamic studies as primary endpoints. Figure 2 shows both individuals and averaged values of these factors.

Although there was some variability in the individual response to the medicine administration as registered by Qmax and Qave changes (Fig.s 2a and 2b, respectively), there were no marked changes in either averaged parameter. As a matter of fact, the analysis showed that there were no statistically significant changes in urodynamics (Table I).

The value of Qmax after true medicine treatment was 20.7 ± 6.1 ml/sec, and the value after placebo treatments was 19.7 ± 7.3 ml/sec. The value of Qave after true medicine treatments was 13.3 ± 3.3 ml/sec and the

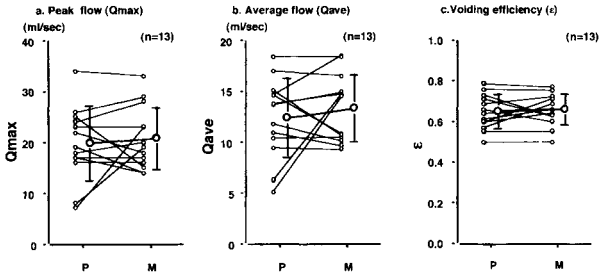

Figure 2. Peak flow (Qmax,a), average flow (Qave,b), and voiding efficiency (ε,c). Every figure is a comparison of values after administration of *Ma-Huang-Fu-Zi-Xi-Xin-Tang* capsules (M) or placebo (P) to younger healthy volunteers . In smaller open circles, average in large open circles and S.D. on error bars.

Table I. Statistical analysis of primary endpoints in urodynamic study after administration of *Ma-Huang-Fu-Zi-Xi-Xin-Tang* capsules (M) or placebo (P).

	mean±S.D.	statisical power, %	results*	95% confidence interval % of difference
Peak Flow (Qmax.) [ml/sec]	P 19.7±7.3 M 20.7±6.1	45	n.s.**	-16.7~26.9
Average Flow (Qave.) [ml/sec]	P 12.4±3.9 M 13.3±3.3	42	n.s.**	-13.3~28.8
Voiding efficiency (ε=Qave/Qmax)	P 0.65±0.09 M 0.66±0.08	99	n.s.**	- 5.1~ 7.4

M : Ma-Huang-Fu-Zi-Xi-Xin-Tang capsule. P : placebo
*: results obtained by imbalanced analysis of variance by the 2 columns and 2 drugs method.
**: n.s.-not significant

value after placebo treatments was 12.4±3.9 ml/sec.

Neither individual nor averaged ε=Qave/Qmax was influenced by medicine administration (Fig. 2c). The value of ε=Qave/Qmax after Mbst treatment was 0.66 ±0.08, and the value after placebo treatment was 0.65 ±0.09. Thus, no effect of the medicine was revealed at any endpoint (Table I).

ANOVA of the 3 primary endpoints, (peak flow (Qmax), average flow (Qave), voiding efficiency (ε =Qave/Qmax), revealed no statistically significant differences in the effects of the medicine, regardless of the order of administration. It is noteworthy that the statistical power of ε=Qave/Qmax was 99%, which means that ε=Qave/Qmax appeared to be one of the strongest indicators for urinate disturbances. The confidence intervals (CI) of the 3 endpoints are also provided in Table I, i.e., -16.7-26.9% for Qmax, -13.3-28.8% for Qave, and -5.1-7.4% for ε =Qave/Qmax.

Detailed analysis of changes in ε=Qave/Qmax in response to medicine administration is presented in Table II.

In the study using elderly persons, peak flow (Qmax) changed from 15.3 ± 4.8 to 15.3 ±8.6. (Fig. 3a), average flow (Qave) changed from 9.4 ± 2.5 to 8.8 ± 4.2 (Fig. 3b), and voiding efficiency (ε) changed from 0.6 ± 0.1 to 0.6 ± 0.1. (Fig. 3c).

No significant difference was shown between prior and following administration of Mbst to elderly persons.

Discussion

Ephedrine is well-known to have a sympathomimetic

Table II. The analysis of variance in voiding efficiency (ε) of before and after administration of *Ma-Huang-Fu-Zi-Xi-Xin-Tang* capsules (M) or placebo (P).

Source of Variance	Sum of Squares	Degree of Freedom	Mean of Squares	F-ratio	5% Critical region	α
Between Subjects	0.1322	11	0.0120	5.461	2.82	0.004
Group or Sequence	0.0001	1	0.0001	0.005	3.23*	0.943
Subjects/Group	0.1321	11	0.0120	5.458	2.82	0.005
Period unadj.	0.0008					
Periods adj. for Drugs.	0.0003	1	0.0003	0.133	4.84	0.722
Drugs unadj.	0.0004					
Drugs adj. for priods	0.0008	1	0.0008	0.342	4.84	0.571
Residual	0.0242	11	0.0022			
Total	0.1576	25				

*10% Critical region.

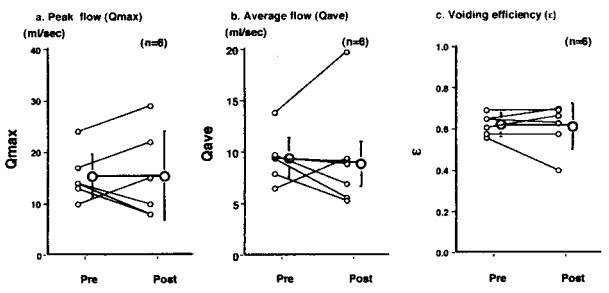

Figure 3. Three indexes that are peak flow (Qmax, a), average flow (Qave, b), and voiding efficiency (ε, c) from the results of studies for elderly persons (n=6). These figures shows comparison of values changed by Pre and Post as shown in figure 2. Each value is shown in small circles, and each average value is shown in large circles with S.D. on error bars.

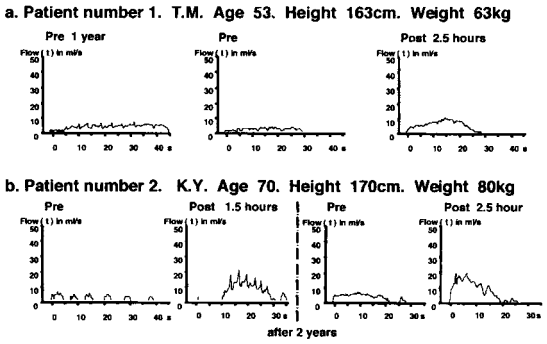

Figure 4. Two cases of urodynamic changes after unfortunate administration of *Ma-Huang-Fu-Zi-Xi-Xin-Tang* capsules (M) to 2 patients with urinate disturbance because of severe benign prostate hyperplasia.

Fig.5a Fig.5b

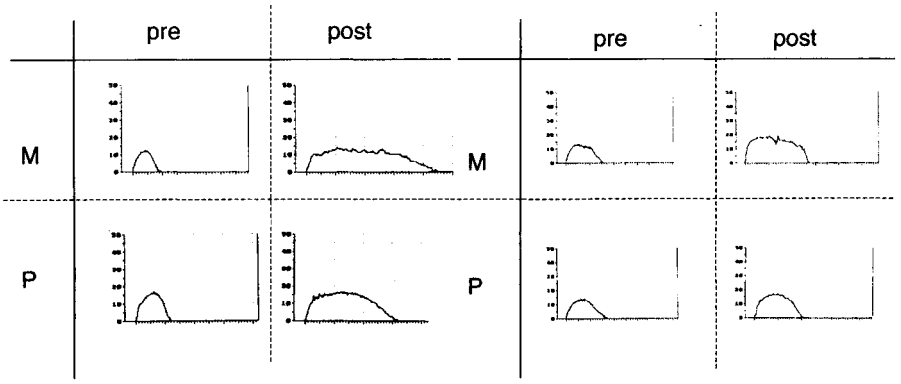

Figure 5. The uroflograms of 2 younger volunteers whose uroflographs showed changeful figures.

effect on vascular, digestive, nervous, and respiratory systems, through adrenergic receptors. So it may increase resistance to the outflow of urine by stimulating the α-adrenergic receptors of smooth muscle cells in the bladder base, which is innervated by both sympathetic and parasympathetic nerves.[2)]

Bladder and sphincter are innervated in a complicated way. The bladder base is innervated by both autonomic nerves. Trigone is innervated by only the sympathetic nerve. Neck and aphincter are innervated by parasympathetic nerves.[1)]

Thus, ephedrine is contraindicated for patients with difficulty in urination, for example, for those with BPH. In addition to ephedrine, there are many other medicines that may increase urinary disturbance, for example, propantherine. These medicines that have sympathomimetic effect by blockage of cholinergic receptor may weaken contraction of bladder smooth muscles.[7)] Thus we often find BPH by administration of these medicines.

We found 2 cases of urodynamic changes after administration of Mbst (containing ephedrine) to patients with urinate disturbance because of severe benign prostate hyperplasia (Fig. 4a,b) by chance. Unfortunately, we could not find a hyperplastic prostate with complaint of urinate disturbance before urodynamic study, not ischuria but prolongation of voiding time by enlargement of voiding volumes. Both urodynamic curves revealed higher increase in peak flows (Qmax), and in average flows (Qave) after administration of Mbst than without Mbst. In case 3a, Qmax with and without Mbst was 12ml/sec, but Qave with Mbst was 7.1 ml/sec then Qave without Mbst was 6.6 ml/sec. Also in case 3b, Qmax with Mbst is 7 ml/sec compared to Qmax without Mbst, which was 9 ml/sec, but Qave with Mbst was 5.6 then Qave without Mbst was 4.0.

We could not easily conclude whether urinate disturbances were improved or not. Such cases made us wonder why administration of Mbst does not worsen urination of elderly persons.

We have shown two cases that at a glance seem to be affected badly by Mbst, but detailed analysis reveals no change in the uroflograms of younger volunteers (Fig.5). One case showed a lowering of peak flow after drug administration, but proportion and ε=Qave/Qmax do not get worse (Fig 5a). In this case, a lower peak of uroflogram occurred with a small amout of urinate volume less than 150 ml. Another case showed plateau figure in uroflogram after administration (Fig.5b) and seemed to worsen the proportion and urinate factors. The change might be caused by a large amount of urination and plateau peak meaned the limit of urinate flow due to diameter of the urether.

In the first selection of volunteers for our study, we were afraid increasing urinary disturbance would be the main side effect of Mbst in administration to elderly persons in Japan. So we decided to start with a study using young volunteers of 38.0 $\pm$ 6.0 years (mean $\pm$ S.D., ranged from 31 to 47 years). After this study, we will prepare a study using elderly volunteers with or without enlarged prostate glands, since we want to ensure the safety of this medicine for all volunteers.

Patients without verified prostate hyperplasia are prescribed ephedrine for the common cold, asthma, or hypotension. In our study, we found that volunteers who

had no urinary disturbances showed a large variation in prostate size (15.6±6.9 g; N=13). Thus, we suppose that there is a possibility that ephedrine-containing medicines may be prescribed for patients with asymptomatic prostate hyperplasia. As a consequence, it is difficult to anticipate the urinary disturbance and nocturia of male patients, when we prescribed ephedrine. On the other hand, we have often seen the opposite phenomenon due to the administration of some kinds of ephedrine-containing Chinese medicines. This was discovered by chance when elderly patients who caught colds were administered Mbst and told us they experienced remission in difficulty of urination even before we found prostate hyperplasia. These patients also noticed a decrease in nocturia. Using Mbst for bronchitis, asthma, hypotension, allergic rhinitis, and so on, we have often seen cases in which urinate disturbance is improved with an increase in voiding volume during administration of Mbst.

The usual dosage of ephedrine at which it affects atonic reaction and sphincter muscles shown by tonic reaction is 10-20 mg in adults.[3] Although Mbst includes 10.0 mg ephedrine, which is a small dosage than usual, Mbst is sufficient to lighten the clinical symptoms of respiratory inflammatory disease. *Ma-Huang-Fu-Zi-Xi-Xin-Tang* is a decoction made from 3 crude medicines, *Ephedra sinica Stapf herb*, heat-treated tuber of *Aconitium carmichaeli Debeaux and Asiasarum sieboldii F. Maekawa* root. *Ma-Huang-Fu-Zi-Xi-Xin-Tang* capsule includes the dried powder from decoction. Although heat-treated tuber of *Aconitium carmichaeli Debeaux* and *Asiasarum sieboldii F. Maekawa* root are thought to enhance the effects of ephedrine on respiratory symptoms, we did not notice any ephedrine-like action of these components on the urinary system.

Recently, some interesting reports about endocrinologic effects and histological differences in the hyperplastic prostate gland have been published.

Carter PG *et al.* reported the relationship between atrial natriuretic peptide (ANP) and nocturnal polyuria in 31 elderly males.[9] In this report, ANP is as important as cholinergic effects on the prostate gland. Based on this report, although Mbst affects the prostate causing urinary disturbance by sympathomimetic effect, we suggest that patients with BPH get better through other endocrinologic effects such as ANP.

Ichiyanagi O. *et al.* reported the relationship between patterns of urinary disturbance in benign prostatic hyperplasia and histological ratio of fibrosis in prostate tissue.[10] They reported a weak relationship between prostatic volume and degree of urinary disturbance.

Qmax and Qave are the most commonly reported values in urodynamic studies. In a report by Nishimoto *et al.*,[4] it was indicated that Qmax and Qave are closely related. Both Qmax and Qave become lower at a voiding volume of over 400 ml.[5] Thus, Qmax and Qave are related not only to the urethral stenosis but also to bladder function. ε=Qave/Qmax was introduced by Nishimoto *et al.* as a value, in contrast to Qmax and Qave to be evaluated separately, which allows evaluation of urethral stenosis independent from bladder functions, such as voiding volume. However, recently, we found some reports on bladder outlet obstruction,[10] which is evaluated by detrutor pressure at Qmax. However, since we were not concerned about bladder pressure in this report, we have recognized only the factors of Qmax and Qave in urinary disturbance. So we used them as supplementary factors for evaluating urinate disturbance.

In the present study, the statistical power of Qmax and Qave was not satisfied and showed no significant difference after medicine administration. Voiding volumes decreased by an average of 20% but also showed no significant differences. Only voiding efficiency ε=Qave/Qmax showed satisfactory statistical power as compared with other factors and had a narrow confidence range. Nishimoto reported an ε=Qave/Qmax value of 0.689 ± 0.03 in the normal group, which is comparable with our results i.e., 0.665 ± 0.05 in ε=Qave/Qmax before administration.[4] The power of ε=Qave/Qmax is greater than that of other factors because the normal value of ε=Qave/Qmax are put into a narrow range. The accuracy of the statistical method was further improved by the crossover test.

In conclusion, we found little effect on urodynamics by Mbst, which included much ephedrine, although ephedrine itself has the side effect of increasing urinate disturbance in prostate hyperplasia. In addition, voiding efficiency ε=Qave/Qmax is a useful factor in evaluating urethral stenosis.

和文抄録

目的：エフェドリン含有漢方薬が，若年者のみならず

高齢者においても，その交感神経刺激作用にもかかわらず，排尿に多大な影響を及ぼさないことを尿流量試験を用いて示す。

方法：麻黄附子細辛湯エキスカプセル（Mbst）とプラセボ（P）による尿流量に対する効果のクロスオーバー試験を13名の若年ボランティア（平均38.0 ± 6.0歳，31〜47歳）に行った。対象の前立腺の推定平均重量は15.6 ± 6.9 g。エフェドリン含有製剤の一例として麻黄附子細辛湯を用いた。なお，コタロー麻黄附子細辛湯カプセルは，味覚や外見上プラセボが作成しやすかったため対象に採用した。尿流量試験は，MbstやPの投与前に一回，投与3時間後に一回それぞれ施行した。最大尿流量率（Qmax），平均尿流量率（Qave）及びvoiding efficiency ε=Qave/Qmaxを指標とした。我々は，無症状の被験者に対して以上の実験を施行することで実験の安全性を確認した後，高齢者に対して麻黄附子細辛湯投与前後の尿流量試験の比較実験を施行した。

結果：MbstとPの投与後のvoiding efficiency ε=Qave/Qmaxは0.66 ± 0.08と0.65 ± 0.09。最大尿流量率は各々20.7 ± 6.1と19.7 ± 7.3 ml/sec，平均尿流量率は13.3 ± 3.3と12.4 ± 3.9 ml/secであった。それゆえ，どのエンドポイントにおいても薬剤による影響は認められなかった。各エンドポイントの中でも ε=Qave/Qmaxが排尿困難の最も良い指標と考えられた。

また，高齢者での尿流量試験でも薬剤投与前後において排尿に影響は認められず，若年者と同じ傾向を示した。

結論：エフェドリンを含有する麻黄附子細辛湯は，若年者のみならず高齢者に対してもそれほど多大な悪影響を来さないことが統計学的に示された。加えて，voiding efficiency（ε=Qave/Qmax）は，尿道狭窄の有用な指標であることが示された。

*〒530-0001 大阪市北区梅田1-11-4
大阪駅前第四ビル2階12号室　青木診療所　青木良純

References

1) Walsh, *et al.*: Campel's Urology. 6th edition, pp. 150-154, 1995.
2) Goodman's and Gillman's : The pharmacological basis of therapeutics 9th edition. MacMiller Publisher's Inc. p. 221, 1996.
3) Diokno, AC. and Taub, M.: Ephedrine in treatment of urinary incontinence. *Urology.* **5**, 624-625, 1975.
4) Nishimoto, K., Iimori, H., Ikemoto, S., *et al.*: Criteria for differentiation of normal and abnormal uroflowmetrograms in adult men. *Br J Urol.* **73**, 494-497, 1994.
5) Siroky, MB., Olsson, CA., Krane, RJ.: The flow rate nomogram: I . DEVELOPMENY *Journal of Urology.* **122**, 665-668, 1979.
6) Ito, T., Imamura, F., Iijima, Y., *et al.*: Gas chromatographic / mass spectrometric determination of plasma and urine levels of ephedrine isomers in human subjects given a Chinese traditional drug. (Mao-Busi-Saisin-To). *Iyakuhin Kenkyu.* **22**, 416-419, 1991.
7) Castleden, CM., Duffin, HM., Briggs, RS, Ogden, BM.: Clinical and urodynamic effects of ephedrine in elderly incontinent patients. *J Urol.* **128**, 1250-1252, 1982.
8) Shenot, PJ., Chancellor, MB., Rivas, DA., *et al.*: In-vivo whole bladder response to anticholinergic and musculotropic agents in spinal cord injured rats. *J Spinal Cord Med.* **20**, 31-35, 1997.
9) Carter, PG., Cannon, A., McConnell, AA., Abrams, P.: Role of atrial natriuretic peptide in noccturnal polyuria in elderly males. *European Urology.* **36**, 213-220, 1998.
10) Ichiyannagi, O., Sasagawa, I., Ishigooka, M., Suzuki, Y., Nakada, T.: Relationship between urodynamic type of obstrution and histological component of the prostate in patient with benign prostatic hyperplasia. *European Urology.* **36**, 203-206. 1998.